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ALLERGIC CONTACT DERMATITIS AND SESQUITERPENE LACTONES

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Synantherologists suffering from sleepless nights brought on by constant itching and redness of the skin may find that their present dilemma is caused by a certain class of chemical constituents present in their favourite family - the Compositae. Our recent clinical experience at the University of British Columbia has established that a plethora of sesquiterpene lactones (isoprenoid derivatives present in taxa of all tribes of the Compositae with the exception of the Tageteae) are the major haptens involved in the formation of skin antigens (protein-hapten complex) that elicit delayed hypersensitivity reactions in man.

In this brief account we summarize the distribution of some sesquiterpene lactones known to cause allergic dermatitis, elaborate on the proposed mechanism of action of lactones and conclude with some comments on the objective(s) of an international group composed of dermatologists, phytochemists, taxonomists and immunochemists that are trying to find solutions to the control of aggressive weeds that cause dermatitis and treatment of people suffering from contact allergy.

Allergic contact dermatitis (poison-ivy or weed dermatitis)

Most people are familiar with allergies brought about by proteins (allergens) present in the pollen of Compositae species (e.g., hayfever from Ambrosia spp.). Dermatitis resulting from exposure to small molecular weight constituents of higher plants is more widespread than

previously imagined. There are two major forms of contact dermatitis recognized. Irritant contact dermatitis resulting from exposure of the skin to plants such as Euphorbia spp. and species of Ranunculus spp. affects all individuals if the amount and duration of the exposure is sufficient. Allergic contact dermatitis results from exposure of the skin to constituents of Toxicodendron (poison-ivy), Primula obconica and members of the Compositae, and only affects some individuals who acquire a specific altered capacity to react to the plants. Such a capacity is not present at birth, but is acquired by postnatal exposure. Specificity for the micromolecular compounds (e.g., pentadecylcatechol in poison-ivy and sesquiterpene lactones in Compositae) designated as haptens (allergens), depends upon an altered immunological status of the individual and is mediated by sensitized T-lymphocytes rather than by antibody. This cell-mediated hypersensitivity is presented clinically by redness, vesiculation (small blisters within the dermis) and itching (1).

Pathogenetic mechanism of allergic contact dermatitis

Following initial contact with a plant that contains a chemical compound which is capable of producing cell-mediated hypersensitivity, a process of sensitization occurs in some individuals and, during the course of a minimum of six days, T-lymphocytes located in lymph glands become sensitized and are released into the blood stream. Following subsequent exposure to the specific sensitizer, circulating lymphocytes accumulate at the site where the antigen (allergen) is sequestered and destroy the cells. Dermatitis becomes manifested one to two days later at the skin site of re-exposure. Such a delay in the appearance of dermatitis at the site of re-exposure is indicated by an alternative term for the reaction, namely "delayed hypersensitivity." The pathogenetic mechanisms of allergic contact dermatitis are summarized in Figure 1.

Detection of delayed hypersensitivity

Delayed hypersensitivity may be detected by means of a "patch test." A chemical compound or acetone leaf extract is applied to the skin, by necessity in a non-irritant dose, and the skin site is examined 48 hours later; a positive patch test reaction, provided nonspecific irritancy is excluded, indicates a state of delayed hypersensitivity. This is a deliberate elicitation, under controlled conditions, of allergic contact dermatitis and part of the clinical investigation of affected patients.

Distribution of sesquiterpene lactones known to cause dermatitis

Sesquiterpene lactones from species of the Compositae, Lauraceae, Magnoliaceae and from the liverwort, Frullania (Jubulaceae) have been shown to be a major class of allergens causing allergic contact dermatitis in humans (2-4). Over eighty lactones were used in patch tests to determine their allergenic potential, and the presence of α -methylene group exocyclic to the γ -lactone, was shown to be the principal immunochemical requisite for the production of dermatitis. One of the allergenic lactones was the pseudoguaianolide, parthenin, the major allergen present in the leaf trichomes of Parthenium hysterophorus L. (5). This extraordinarily aggressive weed was

accidentally introduced into India and other parts of the subtropical world from the Americas, and in certain cities of India, e.g., Poona, allergic contact dermatitis from P. hysterocephalus has become an important dermatological and public health problem (6-7), affecting thousands of patients. A preponderance of males, in contrast to females and children, was affected by contact with the weed. Differences in the penetration of compounds through the skin may be an explanation for this. Among other plants (Table 1) responsible for dermatitis are tiny epiphytic liverworts of the genus Frullania, which causes dermatitis in forest workers who handle the bark of trees (3,8). The sesquiterpene lactone, frullanolide, identified in these epiphytic plants has been shown to be a potent sensitizer. Similar lactones have been found in species of the liverwort Diplophyllum (9). Many varieties of Chrysanthemum (10-12), Costus Absolute, a perfume material derived from Saussurea lappa (13) and laurel oil, from Laurus nobilis (3) are sources of dermatitis and sesquiterpene lactones have been implicated in each instance (Table 2 presents structures). Certain persons may thus cross-react by skin contact allergy to such diverse plants and plant products as ragweed (Ambrosia), liverwort (Frullania), horticultural plants (Chrysanthemum), perfumes (Saussurea), weeds (Parthenium etc.), and vegetables (Cichorium etc.) from a common denominator, viz., a content of sesquiterpene lactones in the plants and plant products.

Mechanism of action of sesquiterpene lactones

Chemical allergens react with skin proteins to initiate the process of sensitization. Studies on the reactivity of sesquiterpene lactones with some amino acids with nucleophilic side-chains showed that lactones with an exocyclic methylene attached to a lactone were all capable of forming adducts by Michael-type addition (14-15). Alantolactone, the major lactone of Inula helenium, is capable of undergoing such addition with the sulphhydryl group of cysteine, with the imidazole group of histidine and with the ϵ -amino group of lysine, but not with the guanido group of arginine, the hydroxyl of serine or the thio-ether function of methionine (15). It therefore seems that all known allergenic lactones contain an exocyclic α -methylene function which probably conjugates with sulphhydryl groups of skin proteins in cells by a Michael-type addition to form complete antigens capable of producing cell-mediated contact allergic reactions (1).

International study group for dermatitis from Parthenium hysterophorus

A Parthenium research group was formed two years ago and has attracted as correspondents about forty interested individuals representing dermatology, immunology, botany, weed science, phytochemistry, agriculture and more recently, government. The aim of the group is to circulate information by means of a Newsletter, six numbers of which have been sent so far. Material for distribution can be sent to Dr. Mitchell. The actual distribution will be carried out through Dr. E. Rodriguez (Developmental and Cell Biology, University of California, Irvine) to whom inquiries can be made for past numbers

of the Newsletter. A European group has recently been formed for the study of Compositae dermatitis in Europe. Dr. Neil Hjork (Department of Dermatology, Konenhaven, Amts Sygehus Igentofte, 2900 Hellerup, Denmark) is responsible for the Newsletter, which is presently restricted to particular members. Presently the new findings are considered pre-publication and confidential. As this group develops, further information may become available. Communication between the three groups might well prove worthwhile.

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FIRST EXPOSURE TO A CHEMICAL
COMPOUND CAPABLE OF PRODUCING
CELL-MEDIATED HYPERSENSITIVITY

SUBSEQUENT EXPOSURE TO THE SPECIFIC
SENSITIZER RESULTS IN DERMATITIS WHICH
APPEARS A DAY AFTER EXPOSURE

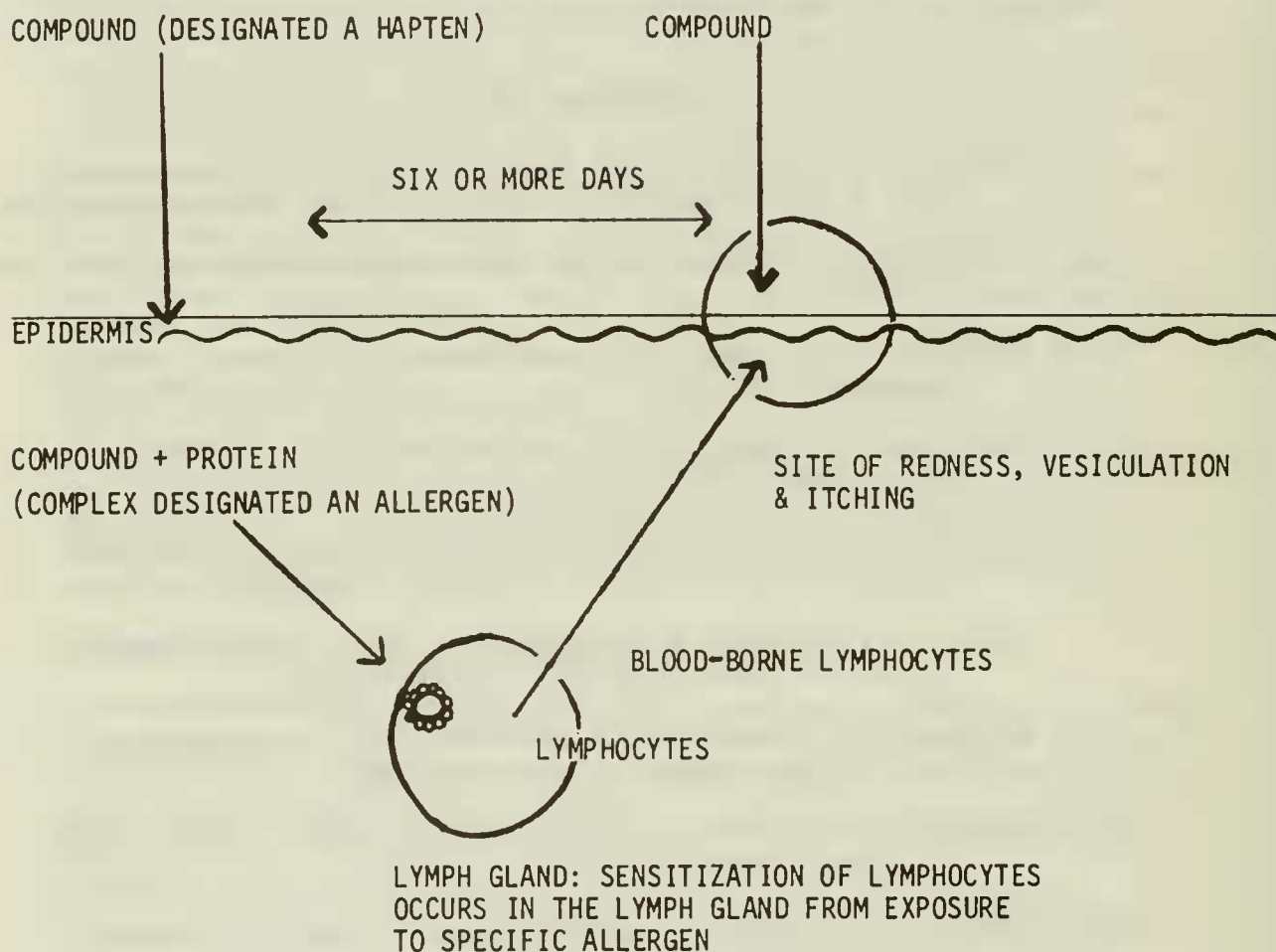
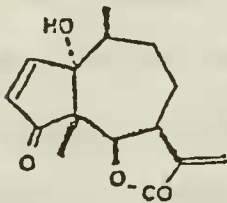
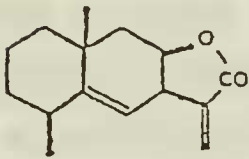
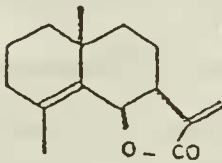
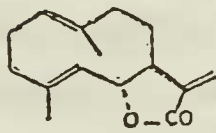
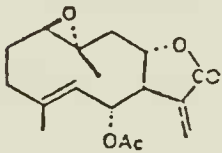
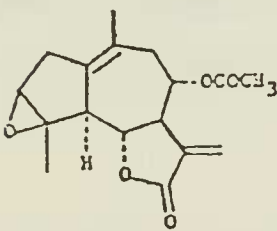


Figure 1. Pathogenetic mechanisms of allergic contact dermatitis (1).

Table 1. Plants of the family Compositae which have been
reported to cause contact dermatitis (1).

Achillea millefolium, Ambrosia spp., Anthemis nobilis, Arctotheca
(Cryptostemma) calendulaceum, Arnica montana, Artemisia spp., Aster
multiflorus, Buphthalmum salicifolium, Cassinea aculeata, Centaurea
americana, Chrysanthemum spp., Cichorium endivia, C. intybus, Cosmos
bipinnatus, Cynara scolymus, C. cardunculus, Dahlia sp., Erigeron
(Leptilon) canadensis, Eupatorium serotinum, Gaillardia sp., Galinsoga
parviflora, Haplopappus (Prionopsis) ciliata, Helianthus annuus,
Helenium autumnale, H. microcephalum, H. tenuifolium, Helipterum
charsleyae, Heterotheca (Chrysopsis) subaxillaris, Hieracium auricula,
Humea elegans, Inula brittanica, I. graveolens, Iva angustifolia,
I. microcephala, I. xanthifolia, Lactuca sativa, L. sativa var.
longifolia, Matricaria chamomilla, Olearia spp., Oxytenia acerosa,
Parthenium argentatum, P. hysterophorus, Pyrethrum (Chrysanthemum) spp.,
Rudbeckia hirta, Rutidosis helichrysoides, Saussurea lappa, Solidago
serotina, S. virga aurea, Tagetes spp., Tanacetum vulgare,
Taraxacum officinale, Telekia (Buphthalmum) sp., Vernonia baldwinii,
Xanthium californicum, X. canadense, X. chinese, X. spinosum,
X. strumarium.

Table 2. Some sesquiterpene lactones reported to cause allergic contact dermatitis in humans (4).

COMPOUND	Plant Source
 Parthenin	<u>Parthenium hysterophorus</u>
 Alantolactone	<u>Inula helenium</u> <u>I. racemosa</u>
 Frullanolide	<u>Frullania tamarisci</u>
 Costunolide	<u>Saussurea lappa</u> <u>Laurus nobilis</u>
 Pyrethrosin	<u>Chrysanthemum</u> spp.
 Arteglaasin-A	<u>Chrysanthemum indicum</u>